Cholestasis

Introduction

Cholestasis is defined by impaired biliary flow (stasis) through ducts lined with cholangiocytes (chole). Cholestasis is always abnormal and pathologic. Bile is continuously produced by hepatocytes. It may be stored in the gallbladder for sudden release into the duodenum, but bile is always flowing—either into the gallbladder (from the liver above) or out of it (into the duodenum below).

Flow through the biliary tree can be impaired in different ways, but three overarching categories—gallstones, autoimmune cholangiopathies, and cancers—make up the majority of cholestatic disease. What makes cholestasis difficult for learners is the way things are named. After you master the material, it isn't difficult to recognize them as different pathologies. But every condition has some kind of "chole" or "biliary" in its name. Worse, some pathologies are named technically, but were named erroneously. So, when you're trying to learn it for the first time, you'll find yourself asking, *"is THAT finding on THIS diagnosis or THAT diagnosis?"* It isn't the learning that's hard; it's the recall. More than usual, we've striven to clearly delineate diseases and NOT build tables comparing them. Absolutely do not build tables that compare diseases with similar-sounding names. That table will be your memory. And, having all the elements of both in that one memory, you will have built a memory of confusion.

We start with cholestasis in general as a pathological and histological process, then demonstrate cholestasis as a clinical syndrome. From there, we go into specific cholestatic diseases: gallstone spectrum, autoimmune cholangiopathy, cancer.

Cholestasis in General

In the last lesson, we covered the approach to laboratory differentiation between prehepatic, posthepatic, and intrahepatic causes of elevated bilirubin. When the cause of bilirubin elevation is cholestasis, it isn't just that there is an accumulation of bilirubin, but an accumulation of all the products excreted in the bile. Cholestasis is the definition of poor bile flow, which in turn leads to the accumulation of not only bilirubin, but **bile salts**, **cholesterol**, and other waste products that are too hydrophobic to be eliminated by the kidneys via urine.

Regardless of the cause of cholestasis, the distinguishing **histological** finding is an **accumulation of bile pigment in the hepatocytes**. For most of the conditions we will consider in this lesson, a biopsy of the liver is usually NOT indicated. But because we are studying Basic Sciences, you will be expected to know what the liver would look like on a biopsy. In cholestasis, bile backs up. Where it backs up first is around the portal triad. Bile pigment usually does not accumulate in the hepatocytes because as they make the constituents of bile, they drop it down the chute, and the bile ducts take it away. Bile salts are detergents that emulsify fats in the gut for easy absorption. Cholesterol and bilirubin are waste products. If the bile doesn't flow, toxic accumulation of these bile products kills hepatocytes. **Periportal necrosis** (hepatocytes dying because of toxic accumulation around the portal triad) and **bile lakes** (accumulation of bile pigment in stretched-out canaliculi) are the hallmarks of cholestatic liver disease. The liver itself in gross will be **green**. When cholestasis happens, it doesn't happen in a small focus of the liver. Whatever the insult is must be distributed across the entire liver. Every portal triad feels the damage, every periportal hepatocyte everywhere. The enzymes in the apical border of the cholangiocytes and hepatic canaliculi are **alkaline phosphatase** (ALP) and **gamma-glutamyl transferase (**GGT). These will be elevated in cholestasis. Because the cholestatic insult is translated back onto the hepatocytes, markers of hepatocellular injury—AST or ALT—can be elevated, although the expectation is to find massively elevated ALP and bilirubin with modest AST or ALT (see Hepatobiliary #4: *Metabolic Liver Disease* for more details).

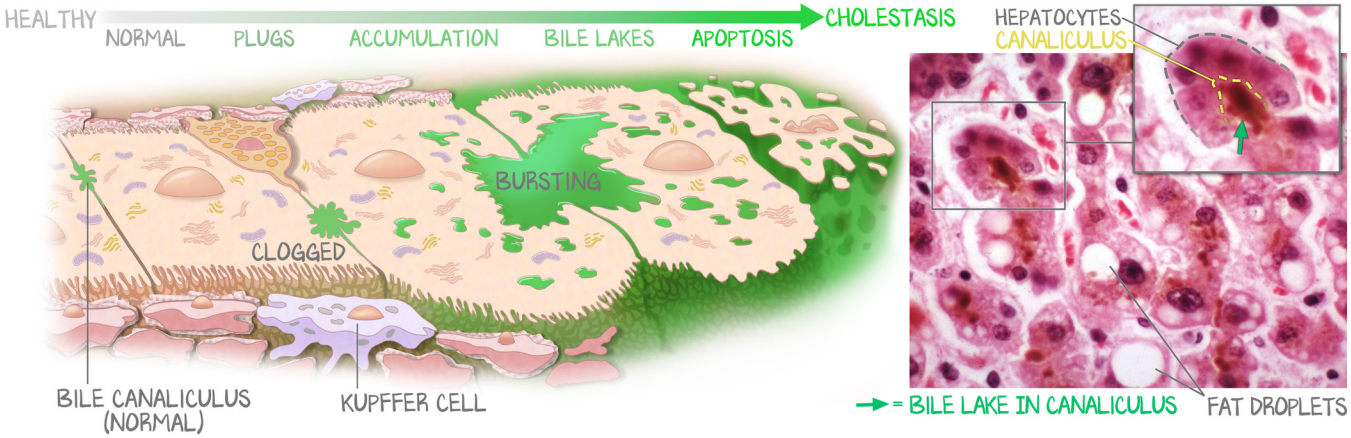

Figure 3.1: Cholestasis
Stagnation of flow through the biliary system causes a backup of pressure. First, the bile canaliculi are clogged. As the hepatocytes attempt to secrete bile salts and dispose of bilirubin, cholesterol, and other components of bile, the hepatocytes are met with a resistance to flow. The hepatocyte tries to drop it down the chute, but the only thing that happens is that it backs up in the hepatocytes' face (figuratively speaking). Without anywhere to go, the bile accumulates in the canaliculi as bile lakes. Eventually, bile spills out of the hepatocyte and into sinusoids. The accumulation of bile in hepatocytes may lead to apoptosis. Bile is darkly pigmented on H&E, whereas the hepatocytes are pink or purple. The inset shows multiple hepatocytes around one bile lake, giving them the appearance of acini of an exocrine gland.

Cholestasis, as a syndrome, can be either acute or chronic. In both cases, the accumulation of **bilirubin** causes **jaundice**. Jaundice is the yellowing first of the oral mucosa (~1.5 mg/dL), then of the whites of the eyes (**scleral icterus** occurs ~2.5 mg/dL), and finally of the skin (~4.0 mg/dL). In both cases, the accumulation of **bile salts** in the skin causes intense **pruritus**. In both cases, because cholestasis is a posthepatic problem, the accumulation of conjugated bilirubin in the urine causes the urine to be dark. Long-term cholestasis (chronic) can result in malabsorption of fat-soluble vitamins, the absence of stercobilin from the stool makes it clay-colored, and the accumulation of cholesterol causes **skin xanthomas**. Short-term cholestasis (acute) does not.

Cholestasis pathogenesis can be divided into intrahepatic or extrahepatic causes.

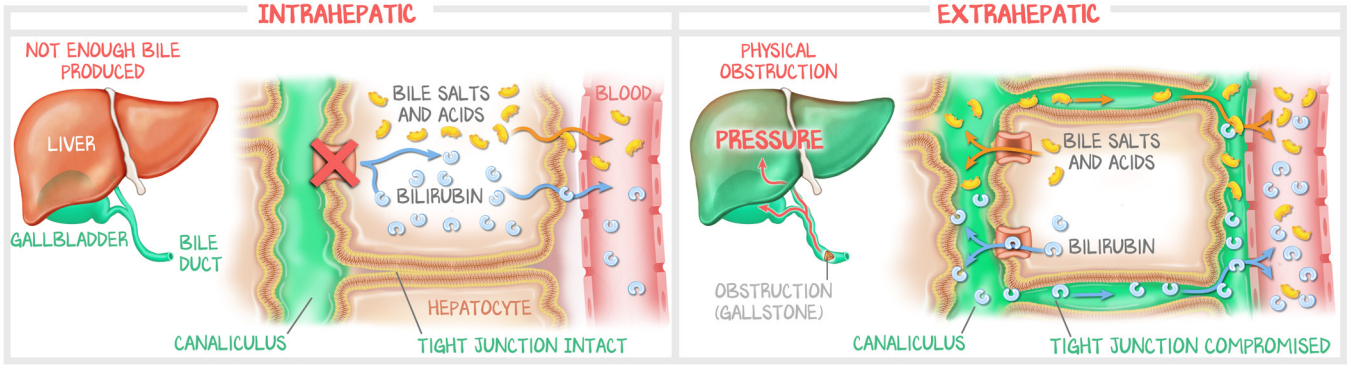

Figure 3.2: Intrahepatic vs. Extrahepatic Cholestasis
Intrahepatic causes of biliary stasis result in the impaired secretion of bile products into the biliary tree, and those products accumulate in the blood. Extrahepatic causes of biliary stasis result in the accumulation of pressure and bile products in the biliary tree, which then spill out into the blood. Either way, bile products end up in the bloodstream.

Intrahepatic causes are usually **metabolic** and intrinsic to the **hepatocytes**. The most common cause of intrahepatic cholestasis is **drug-induced**. Estrogens impair the secretion of bile. Combined oral contraceptives that contain estrogen and progesterone, anabolic steroids, and even pregnancy can cause estrogen-mediated intrahepatic cholestasis. Another cause of intrahepatic cholestasis is **sepsis**. Periportal bile plugs without hepatocyte necrosis are a sign of gram-negative septicemia. Dilated canals of Hering are a marker of septic shock but are not a feature of obstructive causes of cholestasis other than septic shock. Again, you won't be biopsying a liver to check for septic shock, but the morphology of the liver of someone in septic shock will be very different from that of someone with an extrahepatic cause of cholestasis, and a licensing exam may assess that knowledge. One final consideration of intrahepatic cholestasis is primary biliary cirrhosis, discussed below.

Extrahepatic cholestasis means the obstruction of ducts outside the liver. The most common cause of extrahepatic cholestasis is **gallstones**. Obstructions to flow in the bile duct can also be caused by **primary sclerosing cholangitis** (PSC) and **cancer**. The cancers are going to be of the biliary tree (cholangiocarcinoma), parts around the biliary tree (head of the pancreas), or the ampulla itself (ampullary cancer). We now turn our attention to gallstones.

Cholelithiasis (Gallstones)

Bile is supposed to be aqueous. It carries in it lipophilic cholesterol and bilirubin, lipophilic molecules that don't want to be in an aqueous environment. Bile salts keep these substances hidden from the aqueous environment. Without getting too technical, simply assume that if there is too much cholesterol or too much bilirubin, then they will precipitate out and form stones (that is a gross oversimplification, but it works for what you need here).

Cholesterol stones occur when the liver secretes too much cholesterol. Although certainly more than the "four F's" can increase the risk of gallstone formation, the "four F's" help learners remember the major risk factors: **F**emale, **F**ertile, **F**at, and **F**orty (and Native American). They occur in states of increased estrogen—such as being a woman (female)—and even more so during pregnancy (fertile). Obesity (fat), whether in a man or woman, increases cholesterol secretion. And forty is based on incidence—kids don't get gallstones, and the elderly with gallstone symptoms usually have cancer. So it isn't that there is an increased risk due to being in the fifth decade of life; it just reminds the learner that "not young, not old" are the patients who get gallstones. The main constituent of cholesterol stones is, unsurprisingly, **cholesterol**. These stones are **green** on visual inspection. Obesity and race—Western Caucasians, Hispanics, and **Native Americans—**confer the greatest risk.

Pigment stones are so named because they appear black on visual inspection. Pigment stones have, as the main constituent, **unconjugated bilirubin**. Excess unconjugated bilirubin comes from excess red blood cell turnover. Therefore, **pigmented gallstones** occur in patients with hemolytic anemia. The stones are black. Most gallstones are combined and are neither green nor black. All gallstones have the same presentation regardless of their color or risk factors. Symptomatic gallstones cause **colicky pain**. These stones are sharp. When the gallbladder contracts down on them, it causes pain. The gallbladder contracts down in response to CCK, which in turn is released in response to fatty acid contents entering the proximal duodenum. **Right upper quadrant pain, exacerbated by eating**, especially by eating **fatty foods**, is a sign of cholelithiasis. The pain can radiate to the right shoulder. The diagnosis is made with ultrasound; the treatment is surgery, which is done electively. There is a medical therapy for gallstones, urso-deoxy-cholic acid, but it is used only when surgery cannot be performed as it is barely effective.

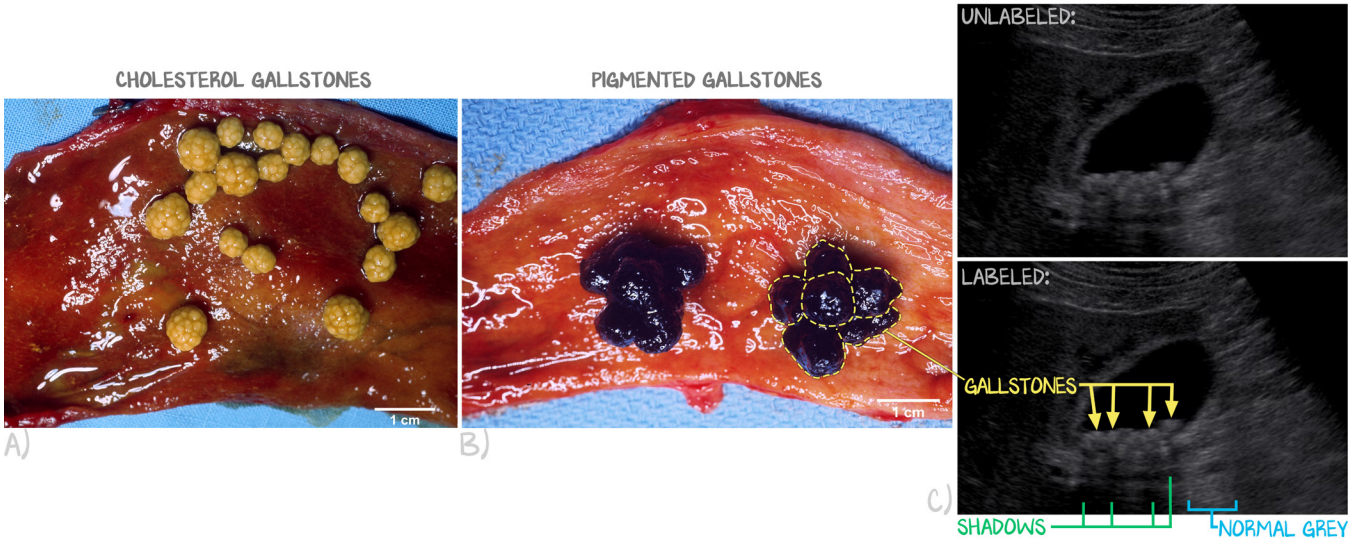

Figure 3.3: Gallstones
(a) Cholesterol stones are green in color. This gallbladder was taken from an elective laparoscopic cholecystectomy and has been opened up, revealing numerous raspberry-shaped, yellow-green cholesterol stones (b) Laparoscopic cholecystectomy specimen showing black stones in the gallbladder. These are pigment stones composed mostly of calcium bilirubinate. (c) Image in long axis showing a gallbladder with multiple gallstones. Gallstones cause shadowing; the radio waves from ultrasound travel well through fluid (black) but bounce off the stones, giving the tissue underneath a darker color. Notice the area of the gallbladder without stones (on either side of the stones), the parenchyma is white. Beneath the stones, it is greyer.

We now discuss the diseases that gallstones can cause.

Gallstone Disease Spectrum

Gallstones are pathologic. There should be no gallstones in the gallbladder normally. When gallstones form in the gallbladder, and those stones don't get stuck in a duct, the diagnosis is **cholelithiasis**. They are intermittently symptomatic, if at all. When a gallstone gets lodged in the cystic duct, it causes inflammation of everything behind the obstruction—the gallbladder—termed **cholecystitis**. Because only the gallbladder is involved, there will be no alteration of liver enzymes. If the stone gets stuck in the common bile duct, it is called **choledocholithiasis** and causes inflammation of everything behind it—gallbladder and liver. Because the common bile duct and the liver are inflamed, the liver enzymes (alkaline phosphatase and bilirubin from the ducts, AST and ALT from the hepatocytes) will be elevated. If the gallstone gets stuck at the hepatopancreatic ampulla (ampulla of Vater), it causes inflammation of everything behind it—gallbladder, liver, and pancreas—called **gallstone pancreatitis**. In addition to the elevated liver enzymes seen in choledocholithiasis, pancreatic enzymes (lipase) will be elevated. Because all of the gallstone diseases cause some degree of cholestasis, and bacteria love stasis, any bacteria that get into that stagnant fluid can grow. A superimposed infection on top of one of these diseases is called **ascending cholangitis**.

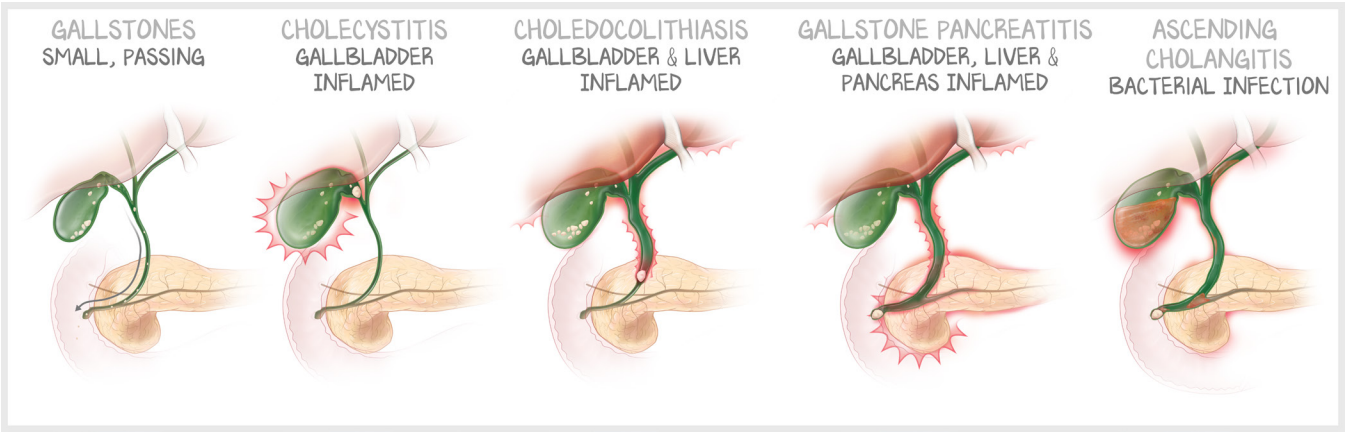

Figure 3.4: Gallstone Spectrum
Moving left to right, this illustration shows a normal schematic of the biliary tree, gallstones in the gallbladder, cholecystitis, choledocholithiasis, gallstone pancreatitis, and ascending cholangitis. Pay attention to where the stone is lodged and notice which organs are affected—those behind the stone. Follow along with the text.

Because gallbladder diseases are usually **acute** presentations, they are often identified and corrected or resolve spontaneously. Therefore, ongoing chronic biliary stasis, which is required to elevate the bilirubin to the double digits, does not occur. Therefore, the elevation in bilirubin will be modest (usually less than 5 and always less than 10), and there won't be the syndrome of pale stools, dark urine, or malabsorption. Acute gallstone disease does not lead to biliary cirrhosis. It gets fixed surgically or resolves spontaneously, or the patient dies of perforation and sepsis.

Cholecystitis. Chole- (bile) -cyst- (bladder) -itis (inflammation). A stone gets lodged in the **cystic duct** and does not pass. The gallbladder behind the stone becomes inflamed. There is "cholestasis" within the gallbladder. Because the stone is not in the common bile duct, the hepatocytes do not feel the obstruction, nor do the cholangiocytes of the common bile duct. Thus, there are no changes in liver enzymes, no jaundice, and there would be no bile lakes on biopsy. There is **constant right upper quadrant pain**. As the gallbladder contracts, the increased luminal pressure causes gallbladder distention and an edematous gallbladder wall. There are mild fever and mild leukocytosis. The patient will present with **Murphy's sign**, which is the arrest of inspiration as the inflamed gallbladder comes into contact with the examiner's finger (or ultrasound probe). Cholecystitis is diagnosed with an **ultrasound**, which should reveal gallstones, pericholecystic fluid, and gallbladder thickening, though rarely the obstructing stone. Fluids and antibiotics against gut flora—anaerobes and gram-negatives—are started. Surgery should not be delayed. Letting cholecystitis "cool off" only provokes more conversions from laparoscopic to open surgery and worsening of the gallbladder necrosis. Histological evaluation will reveal **neutrophils in the lamina propria**. Neutrophils are the cells of acute inflammation, and cholecystitis is the disease of acute inflammation.

Choledocholithiasis. If a stone gets lodged in the common bile duct (above the insertion of the pancreatic duct), the stone will cause true cholestasis: bile lakes and periportal necrosis in the liver. No infection has set up shop yet. The injured hepatocytes release AST and ALT, whereas the cholangiocytes release **GGT and ALP**. Because the bile flow is obstructed, **direct bilirubin rises**. The patient has not yet experienced significant inflammation (no fever or leukocytosis), but the obstruction causes right upper quadrant pain and jaundice. An **ultrasound** will show gallstones in the gallbladder, but there will be evidence of ductal obstruction—a **dilated common bile duct**. The diagnosis is confirmed with an **MRCP** (magnetic resonance cholangio-pancreato-graphy). If a stone is indeed obstructing the lumen, the stone must be removed. This is commonly done by a gastroenterologist, retrieving the stone via ERCP (endoscopic retrograde cholangio-pancreato-graphy)followed by a surgeon removing the gallbladder. The other way the obstruction is alleviated is cholecystectomy and retrieval by the surgeon.

Gallstone pancreatitis. If a stone gets lodged in the hepatopancreatic ampulla, which is below the insertion of the pancreatic duct, the patient will have true cholestasis, as in choledocholithiasis AND pancreatic stasis. The pressure is translated to the liver, so there will be bile lakes and periportal necrosis. Injured hepatocytes release AST and ALT, whereas cholangiocytes release GGT and ALP. Because the bile flow is obstructed, the patient will have right upper quadrant pain and jaundice. In addition, because pancreatic zymogens cannot get out of the pancreatic duct, they activate and begin autodigestion of the pancreas. **Pancreatitis symptoms predominate**—anorexia, epigastric pain, nausea, vomiting—and the **labs reflect pancreatitis**—elevated lipase and amylase. The **ultrasound** will show common bile duct dilation. MRCP confirms the stone is there. ERCP is performed to retrieve the stone.

Ascending cholangitis. Whenever there is stasis, infections can set up shop. If an infection develops behind the stone, and the stone obstructs the ability to flush the infection out, there is nothing to prevent the infection from spreading up through the stagnant fluid. Ascending cholangitis represents a cholestasis just like choledocholithiasis—bile lakes, elevated AST, ALT, GGT, ALP, and direct bilirubin. But more importantly, the **infectious symptoms predominate**. Charcot's triad is right upper quadrant pain, fever, and jaundice. Reynold's pentad, which implies a poorer prognosis, is right upper quadrant pain, fever, jaundice, hypotension, and altered mental status. Treatment of the sepsis— intravenous fluids, gram-negative and anaerobic antibiotics—occurs simultaneously with the evaluation. Ultrasound shows a dilated common bile duct. If the suspicion is high, **emergent ERCP** (notice the skipped diagnostic step of MRCP) is performed to alleviate the obstruction. The presence of neutrophils in the bile ducts is the hallmark of ascending cholangitis.

	CHOLELITHIASIS	CHOLECYSTITIS	CHOLEDOCHOLITHIASIS	GALLSTONE PANCREATITIS	ASCENDING CHOLANGITIS
RUQ pain	Intermittent	Constant	Constant	Constant	Constant
Fever	No	Mild	No	Mild	High
Leukocytosis	No	Mild	No	Mild	High
Symptoms	Worse with eating; radiates to shoulder	Murphy's sign	Elevation of LFTs	Pancreatitis symptoms predominate	Fever Jaundice RUQ pain Hypotension AMS
U/S	Gallstones	Gallstones, pericholecystic fluid, gallbladder edema	Common bile duct dilation	Common bile duct dilation	Common bile duct dilation
Diagnostic step	None	HIDA	MRCP	MRCP	ERCP
Surgery	Elective, laparoscopic	Urgent, laparoscopic	Urgent, ERCP	Emergent, ERCP	Emergent, ERCP

Table 3.1: Gallstone Disease
The symptoms, diagnostic steps, and treatments for each disease.

Biliary Cirrhosis

Biliary cirrhosis describes an end-stage liver (cirrhosis) that appears green (because biliary obstruction causes biliary accumulation in the liver) and got to end-stage because of a biliary problem. Biliary cirrhosis also describes the histological findings of a cirrhotic liver caused by a biliary problem—periportal fibrosis and pericentral sparing. Cirrhosis caused by cholestasis, *biliary cirrhosis*, will cause a **green liver**, indicative that the bile has backed up. Histology will show extensive **feathery degeneration** of the **periportal** hepatocytes, cytoplasmic swelling, often with **Mallory-Denk** bodies (alcohol-induced liver disease and non-alcoholic fatty liver disease will also have Mallory-Denk bodies, but the hepatocytes in this disease are centrilobular, not periportal), and formation of bile infarcts from the detergent effects of extravasated bile. When this autoimmune disease was named primary biliary cirrhosis, it always caused cirrhosis and was secondary to inflammation of intrahepatic ducts. Untreated, it results in biliary cirrhosis, the end-stage anatomy and histology of cirrhosis caused by biliary obstruction. The thing is, with treatment, primary biliary cirrhosis (PBC) rarely leads to cirrhosis. Because the autoimmune cholangiopathy that results from intrahepatic ductal fibrosis is primary biliary cirrhosis, secondary biliary cirrhosis is anything else that is not that specific disease. Therefore, we're going to eliminate any chance of confusion and say that there are two autoimmune cholangiopathies that can result in biliary cirrhosis (the anatomical and histological definition), and that's it. They are primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

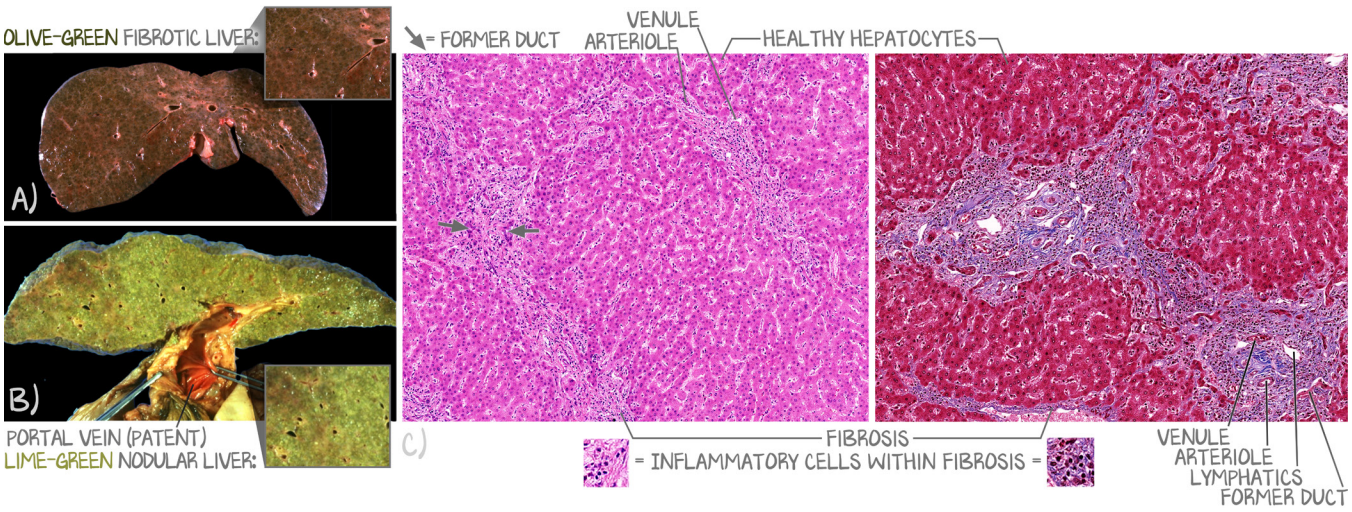

Figure 3.5: Biliary Cirrhosis
(a) An example of a dark green, olive-colored biliary cirrhosis. (b) Another example of biliary cirrhosis with a more lime-green appearance. The portal vein is opened to show that it is patent. Both examples of biliary cirrhosis are considered to be appropriate for biliary cirrhosis. (c) Mild periportal fibrosis without steatosis (no ongoing injury to hepatocytes) and large islands of normal hepatocytes, indicative of portal-based disease. Identify the venule, arteriole, lymphatics, and the former duct on the labeled portal triad, then identify those structures on the unlabeled portal triad.

Autoimmune Cholangiopathies

Biliary cirrhosis is a morphological pattern of end-stage liver disease provoked by chronic cholestasis. PBC is a chronic autoimmune disease that affects intrahepatic ducts, causes intrahepatic cholestasis, and can result in end-stage liver disease with the phenotype of biliary cirrhosis. Primary sclerosing cholangitis (PSC) is another autoimmune disease; this one affects extrahepatic ducts and causes extrahepatic cholestasis, and, like PBC, can also result in end-stage liver disease with the phenotype of biliary cirrhosis. The endpoint of both PBC and PSC is cirrhosis with the morphology of biliary cirrhosis. Other cholestatic diseases can lead to cirrhosis with the morphology of biliary cirrhosis. The confusion arises only with the similarity of nomenclature: PBC and PSC both share "P" and "C" in

their acronyms. They are the two autoimmune cholangiopathies you need to know. Do not learn them as acronyms; learn them by their full names. Any time you see PBC, say in your mind, "primary biliary cirrhosis." Any time you see PSC, say in your mind, "primary sclerosing cholangitis." If you are alone, even say them aloud. We will use the abbreviations, but you should say the whole thing. It may seem like inane instruction, but so many learners conflate the two, so we are purposefully getting ahead of that potential pitfall, not letting you fall victim to what so many before you have.

Primary Biliary Cirrhosis. PBC is an autoimmune disease that affects middle-aged **women**. Think 50 years old, although the range is 30–70. It has a progressive clinical course. It is 95% associated with **antimitochondrial antibodies** (AMA) and sometimes associated with antinuclear antibodies (ANA) and anti-neutrophil cytoplasm antibodies (ANCA). Most cases are diagnosed when asymptomatic, with elevated serum ALP and GGT. When symptomatic, the onset is insidious, presenting with fatigue and pruritus, which increase slowly over time, as does the bilirubin. The disease is confirmed by a **liver biopsy**, which is considered diagnostic if a florid duct lesion is present. **Florid duct lesion** is the proper name for the finding; florid is not an adjective describing a "duct lesion." These lesions are of **small, intrahepatic,** interlobular **ductules**. That means a histology slide is going to be extremely magnified to show you what's going on, and in cross-section, small ductules will be made of only a few cells. The surrounding inflammation collapses the ductules, so the lumen may not be visible. "Inflammation" means that inflammatory cells have entered the tissue. In PBC, there will be many **lymphocytes** surrounding tiny ductules. Normal hepatocytes will surround the lymphocytes. The florid duct lesions are said to be granulomatous because there can be **aggregates of macrophages** within the mass of lymphocytes. Lymphocytes are identified by blue nuclei with little cytoplasm. Granulomatous aggregates of macrophages are multinucleated giant cells with many nuclei within abundant cytoplasm. Look for small ductules, lots of blue dots, then normal hepatocytes around the blue dots.

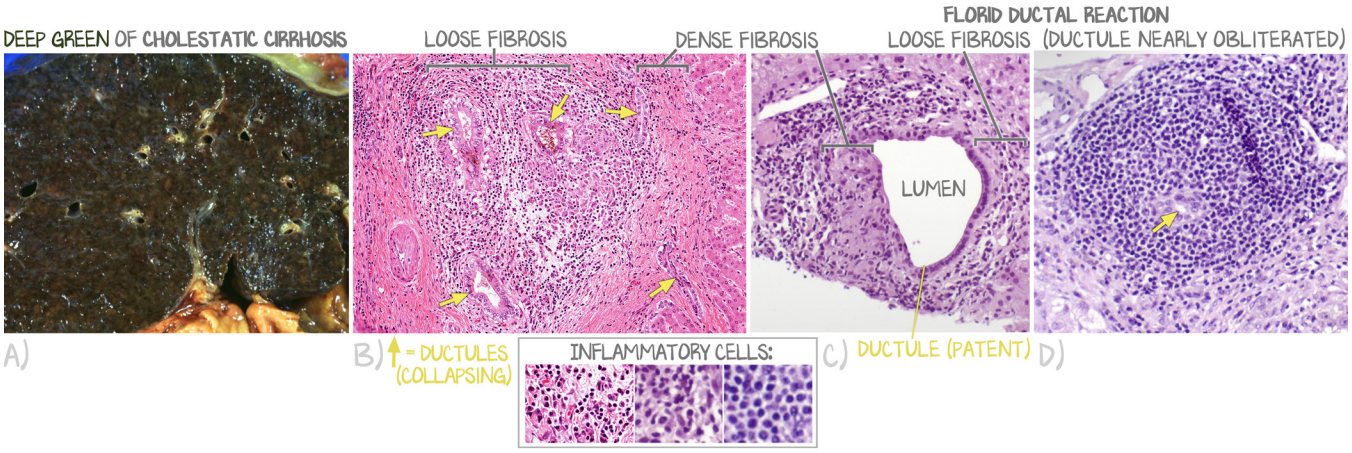

Figure 3.6: Primary Biliary Cirrhosis
(a) Because there are cholestasis and cirrhosis, the liver exhibits the gross appearance of biliary cirrhosis—the liver will be green. (b) Histologically, there will be periductal immune cells in the parenchyma, collapsing small ductules. The inflammatory cells are lymphocytes and multinucleated giant cells. Fibrosis will separate the florid ductal reaction from healthy hepatocytes, seen in the periphery of each image.

Over a period of two or more decades, untreated patients follow one of two pathways to end-stage disease, one in which hyperbilirubinemia predominates and another in which there is prominent portal hypertension. However, the treatment of early-stage disease with oral ursodeoxycholic acid greatly slows the progression of the disease, so most patients now do not reach end-stage liver disease—no cirrhosis. With progression, secondary features indicative of chronic cholestasis may emerge—jaundice, xanthelasmas, steatorrhea, and vitamin D malabsorption-related osteomalacia and/or osteoporosis. For those who do progress to cirrhosis, because there are so few hepatocytes lost and often regenerative

hyperplasia, there is marked **hepatomegaly**, a point of distinction from the shrunken, end-stage cirrhotic livers of chronic viral hepatitis, alcoholism, and non-alcoholic fatty liver disease.

Primary Sclerosing Cholangitis. PSC (did you say primary sclerosing cholangitis or pee ess see?) is an **autoimmune disease** that affects **young men**. Think age 30, although the range is 20–40. It is highly associated with **ulcerative colitis** (UC). Serology is NOT as characteristic of PSC as it is of PBC, although pANCA is found in approximately 65% of patients. It presents in one of two ways. **Asymptomatic patients** get labs for another reason (routine labs for healthy patients or purposeful screening in patients with UC) and find an elevated ALP, which stays elevated on repeat assessment. **Symptomatic patients** have signs of **ascending cholangitis** and get an MRCP to rule in gallstones, but the MRCP shows something very different than gallstones. No ERCP need be performed because PSC is diagnosed **radiologically** with an **MRCP** showing **beads on a string**, a repeated pattern of severe narrowing (stricture of affected ducts), and widening (dilation of unaffected ducts) of the extrahepatic ducts. If an ERCP is done for a biopsy of the extrahepatic ducts or the stricture, there will be **large-duct inflammation** that looks like UC—acute neutrophilic infiltration superimposed on a chronic inflammatory background. That is not very specific, and ERCP has a high chance of causing pancreatitis, so a biopsy of the biliary tree is generally NOT done. What everyone remembers, and what everyone teaches about PSC, is that a biopsy will reveal **concentric onion-skin fibrosis**. What everyone neglects to mention is that the finding is of the **small ducts within the liver**. If you do a LIVER biopsy and HAPPEN to get a sample with the small ducts showing onion-skin fibrosis, the biopsy IS pathognomonic for PSC. This is an extrahepatic disease, and intrahepatic duct involvement is minimal. Therefore, because the likelihood of sampling a small duct on a random sampling of the liver is low, and the risk of liver biopsy high, diagnosis depends on radiological imaging of the extrahepatic ducts and NOT biopsy. There is no specific medical therapy for PSC. Cholestyramine has been used for pruritus, and endoscopic dilation with sphincterotomy or stenting is used for relieving symptoms (Gastroenterology can try stenting, especially if not a transplant candidate). Stenting makes transplantation more difficult (transplant surgeons say don't stent). The disease follows a protracted course of 5–17 years. If transplantation occurs, PSC will recur in the transplanted liver. Ongoing inflammation of the larger ducts **increases the risk of cholangiocarcinoma**. Ongoing cholestasis increases **the risk of biliary cirrhosis**. If the patient also has UC, then the UC increases the risk of colorectal cancer; PSC doesn't increase the risk of colorectal cancer alone.

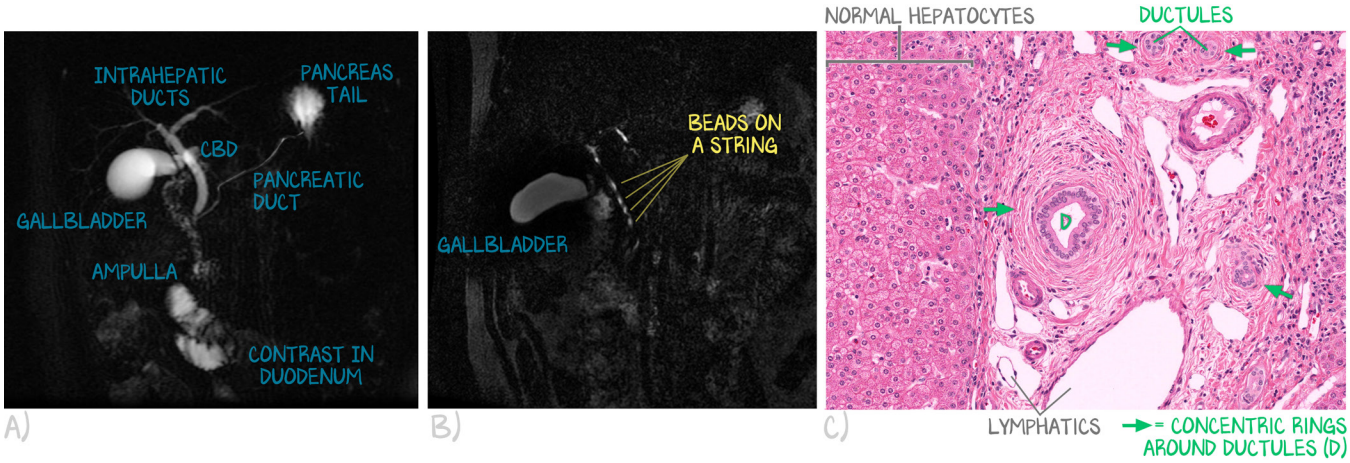

Figure 3.7: Primary Sclerosing Cholangitis
(a) A normal MRCP given for comparison against that of the disease state. (b) MRCP showing the beads-on-a-string appearance of alternating strictures and dilation. (c) The classic histological presentation of primary sclerosing cholangitis (an extrahepatic disease) is periductal concentric "onion-skinning" fibrosis, as shown in the center of this image. There is only sparse inflammatory infiltration. A portal vein tributary is seen at the bottom (large empty-looking space), and a hepatic artery branch is seen on the upper right. You might not see this lesion if you took a liver biopsy from a patient with PSC (which you shouldn't do anyway), as they are rare and NOT likely to be seen on biopsy.

Biliary Carcinoma

Biliary carcinoma is a malignant transformation of cholangiocytes. There are three subsets of biliary carcinoma: intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder adenocarcinoma. The thing is, these are so rare that medical science doesn't have a good understanding of them. It is hypothesized that these represent two cancers. One is a cancer of the cholangiocytes from the canals of Hering (the stem cells of the hepatocytes and intrahepatic ducts that makes intrahepatic cholangiocarcinoma), and the other a cancer of the stem cells of the biliary tree outside the liver (extrahepatic cholangiocarcinoma and gallbladder adenocarcinoma are probably the same disease).

But that's just a hypothesis right now. Genetically, what is known is that the most common mutations found in intrahepatic cholangiocarcinoma—EGFR, the KRAS-PI3K arm, and the BRAF-MAPK arm (more on these in Endocrine and Pulmonary)—are not found in either extrahepatic cholangiocarcinoma or gallbladder adenocarcinoma. Therefore, these are likely two cancers from two distinct stem cell lines that develop through two completely distinct genetic pathways. But that doesn't help you figure out what to learn about this disease.

So here's what to learn. Disregard the fact that there are probably two stem cell populations and everything we know about gene mutations. Right now, our best understanding of cancers of the cholangiocytes is that we either get a biliary tree cancer (cholangiocarcinoma) or a gallbladder cancer (gallbladder adenocarcinoma).

Cholangiocarcinoma (both intra- and extrahepatic) is caused by long-standing inflammation. In general, long-standing **inflammation** leads to cancer. In the United States, long-standing inflammation comes from **autoimmune disease** (PSC). In Asia, where **liver flukes**, such as *Opisthorchis* and ***Clonorchis***, are endemic, the rate of cholangiocarcinoma is higher, and mortality is increased. Any diagnosis of cholangiocarcinoma has a uniformly poor prognosis. The patient will come to the attention of medical care because of obstructive jaundice. MRCP will find the lesion. A biopsy will confirm. Often, little can be done, because the cancer has already metastasized by the time the patient is symptomatic.

Gallbladder adenocarcinoma is a super-rare malignancy that occurs in the elderly, often in the seventh decade of life. They are frequently asymptomatic. On a licensing exam, gallbladder adenocarcinoma will present as a **70-year-old woman with new cholecystitis**. First-time cholecystitis so late in life is the tip-off. The thing is, most of the adenocarcinomas are caused by gallstones. And if someone has symptomatic gallstones in early life, they have their gallbladder removed. Gallbladder adenocarcinoma is at least twice as likely in women as in men, and that ratio is amplified in regions of higher risk (Brazil, India). The classic licensing exam presentation will include a **porcelain gallbladder**, meaning the gallbladder wall is thickened. This makes for a **large, palpable,** and **painless gallbladder** on a physical exam, and there will also be **calcifications** on X-ray. The prognosis is often **worse than cholangiocarcinoma**, as the cancer often has already metastasized or seeded locally.

Citations

Figures 3.3a, 3.3b, 3.5a, 3.5c, 3.5d, 3.7c: Courtesy of WebPathology.

Figure 3.3c, 3.7a, 3.7b: Courtesy of Radiopaedia.

Figure 3.5b, 3.6: Originating from the University of Alabama at Birmingham, Department of Pathology PEIR Digital Library at http://peir.net pursuant to a license grant by the UAB Research Foundation.